Predicting mortality in patients with advanced heart failure: less is often more

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Over one million of new cases of heart failure (HF) are diagnosed every year worldwide. According to the most recent statistics of the American Heart Association (AHA), 6.5 million Americans aged 20 years or older suffer from HF, with a prevalence that is expected to further increase by 46% by the year 2030.[1] Likewise, 15 million people in Europe also suffer from HF, and this number is gradually increasing. The prevalence is especially high in elderly individuals; approximately 2.1% of the overall population aged 65 years or older suffer from HF.[1] Although the global life expectancy has increased by 5 years since 2000 and the mortality for this condition has constantly decreased over the past decade, the 5-year death rate of patients with HF remains higher than 40%.[1] Most notably, the total cost of managing HF in the United States has been estimated at 30.7 billion USD in 2012, and it is likely to further increase to nearly 70 billion USD in 2030.[1] In Europe, HF currently accounts for 1% to 2% of the total health care expenditure.

The analysis of these meaningful figures strongly supports the need to reinforce both preventive and therapeutic measures aimed at limiting the clinical and social impact of this life-threatening condition. This should focus especially on identifying patients at higher risk of unfavorable outcomes, such as acute decompensation, progression towards advanced HF, hospital readmissions, and mortality. Along with a number of demographic and clinical factors, laboratory biomarkers are emerging as attractive means for prevention of, and risk stratification in, HF. The recent joint guidelines of the American College of Cardiology (ACC), AHA, and the Heart Failure Society of America (HFSA) advocate the measurement of some selected biomarkers in different phases of HF.[2] More specifically, the measurement of natriuretic peptides (ie, B-type natriuretic peptide or NT-terminal pro-B-type natriuretic peptide) is recommended for identifying patients at higher risk of developing left ventricular dysfunction or new-onset HF, as well as for assessing disease severity, prognostication, and treatment monitoring. The measurement of other biomarkers of myocardial injury or fibrosis, such as cardiac troponins, galectin-3, soluble suppression of tumorigenicity 2 (sST2), or growth differentiation factor 15,[3] may also be considered for additive risk stratification in patients with chronic HF. Unlike the ACC/AHA/HFSA document, the 2016 guidelines of the European Society of Cardiology (ESC) suggest that early measurement of natriuretic peptide levels can only be useful as an initial diagnostic test, especially when echocardiography is not immediately available or may be used for the screening of impaired ejection fraction.[4] The ESC then concludes that no definitive evidence has been gathered up for recommending the measurement of other biomarkers, such as sST2 and galectin-3, for prognosticating or assessing disease severity in patients with HF.

In this issue of the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Szyguła-Jurkiewicz et al[5] describe the potential association between some hematologic parameters and 3-year mortality in patients with advanced HF. Interestingly, diabetes (hazard ratio [HR], 1.46) enhanced red blood cell distribution width (RDW; HR, 1.05), and decreased relative lymphocyte count (HR, 0.94) were found to be independent predictors of 3-year death in a multivariable Cox regression analysis.

The impact of diabetes on the prognosis of HF has been investigated by numerous previous studies, recently summarized in a meta-analysis of Dauriz et al.[6] They showed that diabetes was associated with a nearly 30% enhanced risk of all-cause and cardiovascular death. Notably, many explanations have been provided for justifying disease progression and outcome of HF in diabetic patients, including enhanced oxidative stress and inflammation, accumulation of advanced glycation end products, and faster progression of coronary artery disease.[7]

There is also strong evidence in support of a causal link between RDW and death in patients with HF, as confirmed by a meta-analysis of Huang et al.[8] They showed that each 1% increase in baseline RDW was associated with a 10% higher risk of future mortality events. Notably, a recent study has also shown that an in-hospital increase of RDW may even be more strongly associated with mortality than the baseline RDW value.[9] Many plausible physiopathological mechanisms have been proposed to explain the unfavorable effect of anisocytosis in HF, including impaired blood flow and decreased oxygenation through the microcirculation, enhanced accumulation of erythrocytes within the vessel wall, and neutralization of vasodilatory mediators.[10]

The most interesting information reported by Szyguła-Jurkiewicz et al[5] actually concerns the inverse relationship observed between lymphocyte count and death in patients with HF. Recently, Carubelli et al[11] conducted a retrospective analysis including 309 patients with acute HF, who were classified according to the median lymphocyte count on admission. In a multivariable analysis, a low absolute lymphocyte count was associated with nearly a double risk of mortality. Similar findings have been recently described by other groups,[12,13] thus inherently confirming that the results reported by Szyguła-Jurkiewicz et al[5] are solid and the role of these blood cells deserves attention in larger prospective studies. Recent evidence suggests that a decreased lymphocyte count, especially of T lymphocytes, should not only be seen as a marker but also as a potential protective factor in HF. These cells are known to regulate smooth muscle proliferation, so that a reduced number of lymphocytes may be associated with less efficient vascular repair and higher progression rates towards decompensated HF and mortality.[14]

The convincing study by Szyguła-Jurkiewicz et al[5] also emphasizes some important aspects that may be useful in laboratory medicine and clinical practice. Many putative biomarkers, especially natriuretic peptides, are emerging as key tools for diagnosis, prognosis, and monitoring of clinical parameters in patients with HF. Nevertheless, these tests are quite expensive, often require dedicated laboratory instrumentation, or, under some circumstances, still need manual and time-consuming techniques, which are unsuitable for timely management of patients, especially those admitted to short-stay units. Unlike these tests, both the lymphocyte count and RDW are parameters automatically measured or calculated by all modern hematologic analyzers.[15] While not imposing incremental costs to the health care system and being available to the vast majority of clinical laboratories worldwide, the clinical significance of their assessment in patients with HF seems now at least as valuable as that of other expensive and time-consuming biomarkers. Less is often more.

Although the clinical use of the lymphocyte count and RDW in HF needs to be confirmed by larger randomized clinical trials, Szyguła-Jurkiewicz et al[5] have provided information that facilitates the design of these forthcoming studies. Likewise, the predictive value of these 2 parameters will need to be assessed in chronic HF with reduced and with preserved ejection fraction.

NOTE The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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